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PATENTS ACT 1977

and

PATENTS (AMENDMENT) RULES 1987

I, Norval O'CONNOR PhD,
translator to RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England, hereby declare that I am conversant with the French and English languages and that to the best of my knowledge and belief the accompanying document is a true translation of the text on which the European Patent Office intends to grant or has granted European Patent No. 0,771,187
in the name of Pierre Fabre Dermo-Cosmetique

Signed this 14th day of January 1999

N. O'CONNOR
For and on behalf of RWS Group plc

The present invention relates to novel compositions which are useful in dermatology and/or cosmetology, these compositions having improved antifungal activity.

The treatment of cutaneous fungal infections is fairly limited due to a lack of therapies. The problems associated with these pathologies - side effects, absence of a response to the treatment or the development of resistance to the microorganisms - are a reality of the field.

Among the skin complaints caused by fungi, those due to yeasts and those due to dermatophytes are distinct.

Skin infections caused by *Pityrosporum* or *Candida* yeasts are once again on the upsurge, in particular due to the increase in skin allergies and to that of the number of patients with an acquired immunodeficiency syndrome.

Specifically, the lipophilic yeasts *Pityrosporum orbiculare* and *Pityrosporum ovale* are present as skin saprophytes, but when they transform into their active hypha form known under the name of *Malassezia furfur*, this results in pityriasis versicolor. This eruption, which is very common in young adults, takes the form of small circular areas with white, pink or brown desquamations. The lesions appear on the trunk, on the proximal part of the arms or the legs and can converge. Good implantation of the microorganism is confirmed when depigmentation of the skin is observed. This is due to the production of a dicarboxylic acid by the yeast, which results from the inhibition of tyrosinase. This effect, which is counter to melanin synthesis, is aesthetically unpleasant and constitutes one of the first clinical indications in the patient, since colonization of the skin by this microorganism is painless.

During treatments, it is essential for all of the regions infested to be included in order to ensure that the problem is eradicated. Patients, subjected to

oral corticoid or immunodeficient therapy, can develop a massive infestation. When a clinical detection is not made and when topical steroids are prescribed, an accelerated eruption can be developed.

Interest in seborrhoeic dermatitis has been rekindled since the arrival on the market of ketoconazole, for the oral and topical treatment of the inflammatory components of this complaint, which is also caused by *Pityrosporum*. This has led to the recognition of a disease which was initially disregarded, but is not recognized as pityrosporum folliculitis. Its main manifestation is a folliculitis of the trunk of young and middle-aged patients, and is frequently associated with seborrhoeic dermatitis.

The latter complaint is in the form of eruptions with greyish desquamations of the scalp, the ears, the inguinal folds, the trunk and the back.

Desquamations on the folds of the eyelids and the nostrils are also a manifestation of attack by this yeast.

It is probable that a very large number of external factors play a role by adversely affecting the saprophytic effects of *Pityrosporum* in pityriasis versicolor and seborrhoeic dermatitis, which induces a change in the skin behaviour of the yeast.

The other yeast pathologies are cutaneo-mucous superficial candidiases. *Candida albicans* is the pathogenic agent most often encountered, but other species can also be present.

Since *Candida* species multiply readily in a hot and humid atmosphere, superficial candidiases locate themselves in the axillary folds or adjacent to the body orifices. Erythemal and humid patches are visible and can give rise to pustules at the margins of the lesions. Needless to say, promoting factors, such as treatment with broad-spectrum antibiotics, systemic steroids and other immunosuppressant molecules, promote the emergence of bucco-digestive candidiases.

Certain forms of diabetes, hypoparathyroidism, can have as a consequence chronic paronychias and require an additional topical treatment.

Lastly, in the case of immunodeficiency, a granulomatous reaction is observed, as in the case of digestive candidiasis. When the patients are severely immunodeficient, both systemic and cutaneous dissemination of the yeast is found.

Besides the irritant effects cited, an immunological response has been described with these yeasts. This is of humoral and cellular order. High levels of anti-pityrosporum seral antibodies during dandruff have been demonstrated.

Furthermore, seborrhoeic dermatitis is most common in patients with an atopic terrain, cervico-cephalic atopic dermatitis, with the presence of specific anti-pityrosporum orbiculare IgE, the level of which is highly correlated with the severity of the disease. As regards dermatophytoses, mention may be made of athlete's foot, tinea and all forms of onychomycosis.

Few treatments are genuinely effective against this array of pathologies.

Imidazole compounds require at least three weeks of a twice-daily regime, the skin lesions often being very extended, and the patient often does not have enough product to treat all of the body lesions (which are visible in particular under black light by the presence of a pale yellow colour). The use of shampoo containing ketoconazole has indeed been put forward to improve the application, but the patient's treatment may fail if a large area of the back is involved. Furthermore, imidazole compounds are fungistatic and the probability of resistance is thus high. EP 0,070,525 describes compositions comprising an imidazole (I) and another substanc chosen from a group which itself comprises crotamiton, which is used in an

amount which is sufficient to dissolve the compound (I).

The oth r local treatments, such as shampoos based on zinc pyrithione, selenium sulphide or coal tar show that remission is not complete after treatment for about one month.

There is thus a real need for an antifungal product which has various qualities such as efficacy, speed of action and excellent skin tolerance.

The present invention thus relates to a novel combination product, the synergistic combination of which has improved antifungal activity, and which is active on strains that are generally resistant to the usual antifungal agents, in particular to imidazole compounds such as econazole.

The present invention also relates to a dermatological and/or cosmetic composition comprising the said synergistic combination of products.

The synergism can be demonstrated by calculating the Fic (fractional inhibitory concentration) or FFC index of a product A which is defined as follows:

$$FFCA = \frac{\text{MFC of the combination product}}{\text{MFC of product A alone}}$$

MFC defining the minimum fungicidal concentration for which a 4.Log 10 decrease of the inoculum inoculated in 5 minutes of contact at 20°C is obtained.

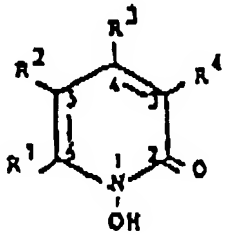
The combination of two antifungal agents A and B is synergistic if the sum of the FFCs (or FFC index) (FFCA + FFCB) is less than or equal to 0.75.

The lower the value of the FFC index, the greater the synergism.

It is considered that there is simple additivity for index values of between 0.75 and 1.1 and

indifference in the interval between 1.1 and 2. Beyond this, the combination is considered as antagonistic.

The novel product according to the invention consists, on the one hand, of an antifungal agent selected from the 1-hydroxy-2-pyridones of general formula I



(I)

in which R_1 represents a saturated hydrocarbon-based residue containing from 6 to 9 carbon atoms,

one of the residues R_2 and R_4 represents a hydrogen atom and the other represents a hydrogen atom or a methyl or ethyl group, and

R_3 represents an alkyl residue containing 1 or 2 carbon atoms,

and their physiologically acceptable salts,

and, on the other hand, crotamiton, as a potentiator of the antifungal activity of 1-hydroxy-2-pyridone.

The dermatological and/or cosmetic composition according to the invention contains, for its part, a synergistic combination of 1-hydroxy-2-pyridone of general formula I as defined above, and crotamiton, with at least one pharmaceutically acceptable excipient.

The term saturated will be intended to mean a hydrocarbon-based residue containing no aliphatic multiple bonds, such as ethylenic or acetylenic bonds.

Preferably, R1 is an alkyl or cycloalkyl residue, and, in this case, a cyclohexyl residue which can be linked to the pyridone ring via an alkylene, or alternatively which can be substituted with an alkyl group.

R1 can also represent an aromatic radical or an aromatic radical linked to the pyridon ring via an alkylene residu .

The aromatic radical is advantageously a phenyl group, optionally substituted with one or more alkyl groups.

Among the compounds of general formula I which are useful according to the present invention, mention will be made in particular of 1-hydroxy-4-methyl-6-n-hexyl-, -6-isohexyl-, -6-n-heptyl- or -6-isoheptyl-2-pyridone, 1-hydroxy-4-methyl-6-octoyl- or -6-isooctyl-2-pyridone, in particular in the form of 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)hydroxy-4-methyl-6-cyclohexyl-2 pyridone, 1-hydroxy-4-methyl-6-cyclohexylmethyl- or -6-cyclohexylethyl-2-pyridone, it being possible in each case for the cyclohexyl residue also to bear a methyl radical, 1-hydroxy-4-methyl-6-(2-bicyclo[2.2.1]heptyl)-2-pyridone, 1-hydroxy-3,4 dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone and 1-hydroxy-4-methyl-6-(β-phenylethyl)-2-pyridone.

Preferably, the 1-hydroxy-2-pyridone is ciclopirox (R1 = cyclohexyl, R2 = R4 = H and R3 = CH3) of octopirox (R1 = 2,4,4-trimethylpentyl, R2 = R4 = H and R3 = CH3), as well as their physiologically acceptable salts, in particular the ethanolamine salts thereof.

The advantage of the 1-hydroxy-2-pyridones lies in their action, on the proteic metabolism of the yeasts; i.e. after they have penetrated into the cell rather than into the synthesis of ergosterol, like the imidazole compounds which act at the parietal level.

Crotamiton, or N-ethyl-N-O-tolylcrotonamide, has, for its part, been described as a scabicide, an antipruriginous agent and as an antifungal agent.

Advantageously, the 1-hydroxy-2-pyridone/crotamiton weight ratio in the combination product according to the invention is between 4/1 and 1/4, preferably close to 1.

The constituents of the novel combination product according to the invention are intended to be used simultaneously.

However, they may also be used in combination separately or offset over time.

The same preferred weight ratio between the 1-hydroxy-2-pyridone of formula I as defined above, and the crotamiton will be desired in the dermatological and/or cosmetic compositions according to the invention.

According to this aspect of the present invention, the synergistic combination as defined above will be present in the composition in a proportion of between 0.5 and 4% by weight.

The compositions are preferably in the form of a shampoo, a lotion or an aerosol solution.

The examples which follow are intended to illustrate the invention without limiting its scope in any way.

In these examples, reference will be made to the attached tables which summarize the fungicidal activity of the products, alone and combined, on econazole-resistant wild-type *Pityrosporum ovale* and *Candida albicans* ATCC 9021.

EXAMPLE 1 : Ciclopiroxolamine/crotamiton combination

Malassezia furfur (Pityrosporum ovale) strains were tested for their sensitivity with respect to the active principles, alone or in combination, according to the invention.

The strains are obtained from the Parasitology Laboratory of the Regional Hospital Centre of Rangueil, Toulouse (France) and a strain is econazole-resistant (eco-R). They were cultured during the tests on solid Dixon medium.

The technique used is original since it uses both the principle of the chessboard technique and that of the Afnor standard by membrane filtration relative

to the fungicidal nature, with a microorganism-molecule contact time of 5 minutes.

This is a macro-method which was thus carried out here, with validations, in each test, of the solvent control for the molecules (20% Tween®, 17% ethanol in distilled water).

This solvent mildly inhibits the activity of ciclopiroxolamine, and better results should thus be expected in practice. The other controls are that of the vigour of the strain and of the efficacy of the products alone, i.e.:

- ciclopiroxolamine 4%
- crotamiton 4%

Table 1 represents the geometric averages of the logarithmic reduction on two wild-type *Pityrosporum ovale* strains, one of which is eco-R, the number of tests and the percentage of efficacy.

The Afnor standard considers that there is a fungicidal nature for a 4 Log 10 reduction of the inoculum after contact for 15 minutes.

We therefore have here after five minutes of contact 100% activity for:

- Crotamiton 4% (product used alone)
- Crotamiton 2% + Ciclopiroxolamine 2% (synergistic combination)

and 50% activity for

- Ciclopiroxolamine 4% (product used alone)

For technical reasons of solubilization of the molecule, we considered that the higher concentrations of ciclopiroxolamine would tend towards 100% activity at about 6% ciclopiroxolamine. The FFC index is thus less than 0.7.

The pH in all of these studies is around 8.

EXAMPLE 2 : Octopiroxolamine/crotamit n combination

The combination of octopirox with crotamiton was tested according to the methodology of Example 1 on an eco-R *Pityrosporum ovale* strain and *C. albicans* ATCC 9021.

Table 2 represents the results obtained on eco-R *P. ovale* after five minutes of contact for the combination:

- crotamiton 1%/octopirox 1%, for which there is 100% efficacy
- whereas the products alone at twofold or fourfold concentrations are less active.

Specifically, crotamiton at 4% gives an efficacy of 84% and octopirox at 2% gives an efficacy of 45%.

It is thus seen that the concentration ratio gives an FFC index of less than 0.75.

The same solvent was used and checked in each test, as specified in the Afnor standard.

These results were confirmed on an Afnor reference yeast (*C. albicans* ATCC 9021). The results are given in Table 3.

The tests in Example 2 were carried out with a more basic pH = 9.

TABLE 1

Products concentrations (%) (m/v)	CPO(4)	CPO(2)	CPO(2) Crota(0.5)	CPO(2) Crota(1)	CPO(2) Crota(2)	Crota(1)	Crota(2)	Crota (4)
Mg	2.05	0.43	1.11	2.90	4.09	0.03	0.77	3.77
n	7	7	3	7	3	7	7	3
% activity	50%	10%	25%	75%	100%	1%	20%	100%

CPO: ciclopiroxolamine

Crota: crotamiton

Mg: geometric mean of Log 10 of the reduction of the number of microorganisms

n: number of independent tests

Syn rgism is seen for CPO 2%/Crota 2%: the products alone, at twofold concentration CPO 4% or Crota 4%, are less active than the less concentrated combined products.

TABLE 2

Products (%)	Octo(2)	Octo(1) Crota(1)	Crota(2)	Crota(4)
Mg	1.85	4.07	1.59	3.26
n	2	2	2	2
% activity	45%	100%	40%	83%

Octo: octopirox

TABLE 3

Products (%)	Octo(2)	Octo(1)	Octo(1) Crota(1)	Octo(0.5) Crota(1)	Octo(0.5) Crota(1)	Crota(2)	Crota(4)
Mg	3.18	0.36	4.94	0.57	2.54	2.43	4.95
n	3	3	3	2	3	3	3
% activity	60%	7%	100%	10%	50%	50%	100%

EXAMPLE 3: Shampoo

Octopiroxolamine	)
or	) 0.5 to 2%
Ciclopiroxolamine	)
Crotamiton	0.5 to 2%
Decylglucoside (55% sol.)	10 g
Disodium cocoamphodiacetate (38% sol.)	15 g
Cocamidopropylbetaine (30% sol.)	
MEA cocamide	5 g
Propylene glycol	2.5 g
Fragrance, dye	
Complexing agent	
Demineralized water qs	100 ml
pH adjusted to between 7 and 9	

EXAMPLE 4 : Shampoo

Octopiroxolamine	)
or	) 0.5 to 2%
Ciclopiroxolamine	)
Crotamiton	0.5 to 2%
Laurylpolyglucose (50% sol.)	10 g
Disodium cocoamphodipropionate (40% sol.)	8 g
Polysorbate-20	1 to 3 g
Hydrogenated talloweth 60	
Myristyl glycol	2 to 3 g
N-hydroxyethylacetamide (70% sol.)	0.5-1.5%
Fragrance, complexing agent	
Opacifier	
Demineralized water qs	100 ml
pH adjusted to between 7 and 9	

EXAMPLE 5: Shampoo

Octopiroxolamine	)
or	) 0.5 to 2%
Ciclopiroxolamine	)
Crotamiton	0.5 to 2%
Decylglucoside (55% sol.)	6 g
Disodium cocoamphodiacetate (38% sol.)	
Cocamidopropyldimethylaminohydroxypropyl	
Collagen hydrolysis [sic] (30% sol.)	7 g
DEA cocamide	3 to 5 g
Glycerol	2 g
Fragrance, dye	
Demineralized water qs	100 ml
pH adjusted to between 7 and 9	

EXAMPLE 6 : Shampoo

Ciclopiroxolamine or octopiroxolamine	)
	) 0.5 to 2%
Crotamiton	)
Triethanolamide alkyl ether sulphate	
(30% sol.)	20 to 50%
Coconut fatty acid dihydroxyethanolamide	
Disodium ethylenediamine	0.15 %
Sodium chloride (qs viscosity)	1%
Fragrance	
Purified water qs	100 g

It is important to ensure that the pH of these shampoos is adjusted to about 7-9 for reasons of efficacy and better solubilization of the active agents. It is clearly understood that these formulations are not limiting and that it is important to promote the compatibility of the surfactants with the 1-hydroxy-2-pyridone/crotamiton combination according to the invention.

EXAMPLE 7 : Hair lotion

Octopiroxolamine	)
or	) 0.5 to 2%
Ciclopiroxolamine	)
Crotamiton	0.5 to 2%
Laurylpyridinium chloride	0.01 to 0.100
Dimethicone copolyol	0.10 to 0.50%
Fragrance qs	
Water/alcohol mixture 30% to 60% vol. qs	100 ml

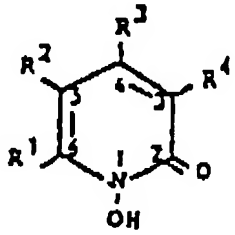
EXAMPLE 8 : Aerosol solution

Octopiroxolamine	)
or	) 0.5 to 2%
Ciclopiroxolamine	)
Crotamiton	0.5 to 2%
Cyclomethicone	1 to 5%
Methylol	30 ml
70% N-hydroxyethylacetamide	1 to 5%
Ethyl alcohol	50 ml
Demineralized water qs	100 ml

Nitrogen qs 9 bar for pressurization in aerosol can.

CLAIMS

1. Combination product, characterized in that it consists of a combination of, on the one hand, an antifungal agent selected from 1-hydroxy-2-pyridones of general formula I:



(I)

in which R_1 represents a saturated hydrocarbon-based residue having from 6 to 9 carbon atoms,
one of the residues R_2 and R_4 represents a hydrogen atom and the other represents a hydrogen atom or a methyl or ethyl group, and R_3 represents an alkyl residue having 1 or 2 carbon atoms,
and their physiologically acceptable salts,
and, on the other hand, crotamiton, as potentiator of the activity of the antifungal agent.

2. Product according to Claim 1, characterized in that, in the general formula I, R_1 is an alkyl or cycloalkyl residue,
it being possible for the said cycloalkyl residue to be linked to the pyridone ring via an alkylene, or alternatively to be substituted with an alkyl group.

3. Product according to Claim 1, characterized in that, in the general formula I, R_1 is an aromatic radical, optionally substituted with one or more alkyl groups, which can be linked to the pyridone ring via an alkylene residue.

4. Product according to Claim 1, characterized in that the antifungal agent of general formula I is ciclopirox or octopirox, as well as their physiologically acceptable salts, in particular their ethanolamine salt.

5. Product according to one of Claims 1 to 4, characterized in that the 1-hydroxy-2-

pyridone/crotamiton w ight ratio is between 4/1 and 1/4, preferably close to 1.

6. Product containing an antifungal agent selected from the 1-hydroxy-2-pyridones of general formula I, as defined in Claims 1 to 4, and crotamiton, as a combination product for a simultaneous or separate use, or for use spread out over time, for the treatment of fungal skin infections.

7. Dermatological and/or cosmetic composition, characterized in that it contains a synergistic combination of a 1-hydroxy-2-pyridone and crotamiton, as defined in Claims 1 to 5, and at least one pharmaceutically acceptable excipient.

8. Composition according to Claim 7, characterized in that it contains between 0.5 and 4% by weight of the synergistic combination.